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EXTERNAL MEMORANDUM

TO: Mark Thompson, Montana Resources

FROM: Michael Garry, Ph.D.

DATE: January 16, 2020

SUBJECT: Review of Meconium Study by McDermott et al. (in press)

We reviewed the McDermott et al. (in press) cross-sectional pilot study that compared concentrations of selected metals in the meconium from 15 Butte, Montana, newborns with that from 17 Columbia, South Carolina, newborns. The focus of our evaluation was on the key findings reported by the authors of this study: what they believe to be higher levels of copper, manganese, and zinc in the meconium of the Butte newborns compared with the Columbia newborns. In particular, we evaluated the following: 1) how levels of these metals in meconium from newborns in these two locations compared with meconium levels in other studies from the published scientific literature; 2) the contribution of different sources to metals exposure in Butte for pregnant women and their fetuses; and 3) whether scientific references cited by McDermott et al. support the statements in their article. Our findings are summarized below, with additional details provided in three attached tables.

Table 1. Comparison of meconium metal concentrations in Butte, MT, and Columbia, SC, reported by McDermott et al. (in press) with data from cited and other studies (µg/kg)

Findings: Concentrations of copper, manganese, zinc reported in ten studies, including those cited by McDermott et al. (in press), were similar to those in Butte newborns and approximately 1,000 times higher than those reported for Columbia newborns.

Table 2. Comparison of copper, manganese, and zinc intake from different sources relevant to pregnant women

Findings: Copper, manganese, and zinc are essential trace elements necessary for growth and maintenance of health. Dietary exposures considerably exceed exposures to these elements from soil and dust, as estimated based on concentrations in Butte soil reported by Hailer et al. (2017), along with U.S. EPA reasonable maximum soil ingestion rates, which also incorporate dust that is inhaled and subsequently coughed up and swallowed. Intake from prenatal vitamins exceeds soil exposures to these elements by over 100 to 1,000 times. Thus, environmental exposures in Butte would have a negligible contribution to fetal exposures to these elements in comparison with the normal maternal diet and especially prenatal vitamins, if taken.

Table 3. Review of McDermott et al. (in press) meconium study statements

Findings: Statements regarding the potential developmental neurotoxicity of copper, manganese, and zinc, as well as assertions that meconium metals levels are much higher in Butte than published values for other locations, are not well supported and in some cases are contradicted by the literature referenced by McDermott et al. (in press).

Table 1. Comparison of meconium metal concentrations in Butte, MT, and Columbia, SC, newborns reported by McDermott et al. (in press) with data from cited and other studies (μg/kg)

	Location	Statistic	N	Arsenic	Copper	Manganese	Molybdenum	Lead	Zinc	Study population
McDermott et al. (in press)	Columbia, SC	Median	17	<1.4	14.68	3.25	<0.7	<0.6	43.34	Full-term births; 2019
	Butte, MT	Median	15	32	26,311	5,364	59	<0.1[a]	81,642	Full-term births; 2019
Haram-Mourabet et al. (1998)	Manhasset, NY	Mean	8–9	NR	90,300	35,800	NR	NR	365,400	Full-term only (pre-term also available)
Arbuckle et al. (2016)	Canada	Median	1,591	NR	NR	4,900	NR	<4[b]	NR	10 cities across Canada; live births; 2008–2011
Ettinger et al. (2017)				<20[c]	NR	NR	NR	NR	NR	
Cassoulet et al. (2019)	Canada	Median	371	123	67,180	14,310	NR	22	313,800	Eastern Townships, Quebec, Canada; live births; 2008-09
Aziz et al. (2017)	Pakistan	Range of means[d]	309[d]	NR	ND (<4,000)–28,700	NR	NR	ND (<2,000)–14,400	9,500–160,300	2 hospitals in Karachi; live births; results stratified by 19 cities of residence
Ostrea et al. (1997)	Philippines	Mean	422	NR	NR	NR	NR	63,900	NR	7 hospital nurseries in Manila; live births
Ostrea et al. (2002)[e]	Philippines	Median	426	ND	NR	NR	NR	17,885	NR	3 perinatal centers in Manila, live births
Gonzáles de Dios et al. (1996)	Spain	Mean	38	NR	36,400	4,100	145	289	76,000	Full-term only (pre-term also available)
Türker et al. (2006)	Turkey	Median	117	NR	116,800	NR	NR	46,500	234,000	Healthy infants; industrial city of Kocaeli; 2001
Hamzaoglu et al. (2014)	Turkey	Median	31	60	71,000	NR	NR	84	229,000	From industrial district (Dilovasi) in industrial city of Kocaeli; 2009-11
			18	70	67,050	NR	NR	41	244,500	From non-industrial district (Kandira) in industrial city of Kocaeli; 2009-11

NR: not reported

ND: not detected

<: not detected at the detection limit listed

[a] Detected in only 1 sample at 5 μg/kg

[b] Not detected in 79% of samples

[c] Not detected in 94% of samples

[d] Range of mean values and N for 18 of 19 cities studied; one city was excluded from this table because metals were not detected in any maternal blood, cord blood, or meconium samples

[e] Meconium metals levels converted from reported units of ng/ml based on 0.1 g of meconium sample reconstituted in 50 ml of water for analysis

Note: Türker et al. (2013) was also cited by McDermott et al. (in press); however, units in Türker et al. (2013) are presented per kg body weight and cannot be directly converted for comparison with other studies and, thus, results are not included in this table

Table 2. Comparison of trace element daily intake from different sources relevant to pregnant women

	Soil Exposure Parameters		*Element Intake from Different Sources*			*Dietary Limits*		
Trace Element	Median Butte Soil Concentration (Hailer et al. 2017) (mg/kg)	Soil/Dust Ingestion Rate (kg/day)	Incidental Soil/Dust Ingestion[a] (mg/day)	Typical Dietary Intake for U.S. Women (mg/day)	Upper Level in Over the Counter Supplements (mg/day)	RDA/AI for Pregnant Women (mg/day)	Tolerable Upper Intake during Pregnancy (mg/day)	Reference for Dietary and Supplement Intakes
Copper	138	0.0001	0.0138	1.1	15	1.3	10	https://ods.od.nih.gov/factsheets/Copper-HealthProfessional/
Manganese	585	0.0001	0.0585	2.2	20	2	11	https://ods.od.nih.gov/factsheets/Manganese-HealthProfessional/
Zinc	243	0.0001	0.0243	9	50	11	40	ATSDR (2005); https://ods.od.nih.gov/factsheets/zinc-HealthProfessional/

RDA: recommended dietary allowance; average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals

AI: adequate intake; intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA

[a] Incidental soil ingestion calculated as the mean residential soil ingestion reported in Butte by Hailer et al. (2017), multiplied by the U.S. EPA reasonable maximum residential adult soil ingestion rate of 0.0001 kg/day

ATSDR. 2005. Toxicological profile for zinc. Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services.
Hailer MK, Peck CP, Calhoun MW, West RF, James KJ, Siciliano SD. 2017. Assessing human metal accumulations in an urban superfund site. Environ Toxicol Pharmacol 54, 112–119

Table 3. Review of McDermott et al. (in press) meconium study statements

Statement	Page/ Paragraph	References Cited as Support	Relevant Information from Cited Reference	Conclusion
"Exposure to lead (Pb),manganese (Mn), arsenic (As),mercury (Hb [sic]) and other metals through inhalation, dermal absorption, and ingestion of contaminated foods, soils, and dust significantly increases the risk for neurodevelopmental disabilities in children exposed in utero or during early childhood."	p. 1/1	Aschner and Costa (2011–2018), McDermott et al. (2014), Al-Saleh et al. (2014), McDermott et al. (2011), Liu et al. (2010), Claus Henn et al. (2017), Rodríguez-Barranco et al. (2013), Ciesielski et al. (2012)	These citations are more general references and do not establish a relationship between metal exposure through soil and dust and neurobehavioral effects, or that levels of exposure in Butte would cause these effects. While some metals, such as As, Pb, Hg, and Mn, have been associated with developmental neurotoxicity at high sufficiently high exposure levels (typically in drinking water for As and Mn), this association has not been demonstrated at the exposure levels that might occur with soil and dust levels measured in Butte. There is less evidence for developmental neurotoxicity for the other metals (Cu and Zn).	References do not support statement
"A study comparing the effectiveness of maternal blood, maternal hair, infant hair, cord blood, and meconium to detect exposure to various toxins, found a higher percentage of exposure by meconium analysis."	p. 2/3	Ostrea et al. (2008)	Ostrea et al. (2008) pertains to organic pesticides, not metals. This statement does not appear to be true for metals. The Canadian cohort (MIREC study; Arbuckle et al. 2016) study that examined metals in maternal blood, cord blood, and meconium reported a higher percentage of detections for maternal and cord blood than meconium for Cd, Pb, and total Hg. All samples of maternal and cord blood and meconium had detectable manganese.	Citation is misleading; should clearly state that cited study does not address metals; McDermott et al. do not acknowledge that the Arbuckle et al. (2016) study does not support this statement for metals
"The relatively low concentrations in the 17 newborns from Columbia are similar to levels reported in other studies of meconium and in the low µg kg−1 range (or less)"	p. 3/4	Arbuckle et al. (2016)	The median meconium Mn level in this Canadian cohort (MIREC study) was 4,900 µg/kg, similar to the median manganese meconium level reported by McDermott et al. (2019) for Butte of 5,364 µg/kg and much higher than the 3.25 µg/kg level reported for Columbia, SC (see Table 2).	Reference does not support statement
		Ettinger et al. (2017)	Arsenic was not detected in meconium in this Canadian cohort (MIREC study) at a relative high detection limit of 20 µg/kg (see Table 2) to conclude arsenic was in the "low µg/kg range or less."	Reference does not support statement
		Aziz et al. (2017)	Reported selected metals in meconium from babies born in Karachi hospitals to low income mothers living in 19 industrial areas. Mean meconium Cu and Zn levels ranged from ND to 28,700 and 9,500 to 160,000 µg/kg, respectively. Mean concentration reported by McDermott for Butte of 28,134 µg/kg for Cu and 109,154 µg/kg for Zn are within these mean ranges (see Table 2).	Reference does not support statement
		Türker et al. (2013)	Units in Türker et al. (2013) are presented as ng/g per kg body weight and cannot be directly converted for comparison with McDermott results.	Reference does not support statement

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"A study from Turkey compared meconium levels of Pb, Cd, Zn, Fe and Cu in preterm surviving and non-surviving fetuses/stillbirths, and reported statistically significant higher metal levels in the non-survivors (Türker et al. 2013). The concentrations in the live births of that study were comparable to the Columbia data and the stillbirths had levels of metals that were actually lower than the measurements made in Butte."	p. 4/1	Türker et al. (2013)	This is a "preliminary study" of meconium in 304 preterm infants showing a higher concentration (reported as ng/g) of Pb, Cd, Zn, Fe, and Cu in the meconium per kg body weight of deceased compared to surviving infants. However, non-surviving infants had much shorter gestational age and birthweight, thereby inflating the meconium concentration when divided by a smaller body weight compared with the larger surviving infants. After restriction to 23 preterm infants born before 30 weeks, only meconium levels of Pb were higher in deceased infants. Comparisons were not adjusted for any confounders. Recruitment was poorly described and participation rates were not reported. Units in Türker et al. (2013) presented in ng/g per kg-body weight cannot be directly converted for comparison with McDermott results. An approximation by multiplying the Cu meconium result of 48.2 ng/g per kg body weight by the average body weight of surviving infants (2.07 kg) results in a concentration of 100 ng/g (μg/kg), which is considerably higher than presented by McDermott et al. for Columbia (14.7 μg/kg). Overall, younger gestational age, as well as likely nutritional deficiency, is expected to result in less accumulation in meconium than for a term infant. Nevertheless, levels for these pre-term infants appear to be higher than reported for Columbia. As we understand, U.S. EPA has confirmed with Türker et al. that the reported units were in error and should have been μg/g, which would result in an approximate Cu meconium concentration of about 100,000 μg/g, which is similar to levels reported earlier by Türker et al. (2006).	Reference does not support statement
"Cu, Zn, and Mn have also been widely distributed throughout Butte, and these metals have been implicated in the literature as potential neurotoxins, especially when exposure is chronic."	p. 4/1	Türker et al. (2013)	Neurodevelopmental outcomes were not assessed in this study, nor was any other type of neurotoxicity.	Reference does not support statement
		Karri et al. (2016)	A review article on the toxicology of Pb, Cd, As, and methyl Hg (not inorganic Hg) exposure and cognitive dysfunction. The authors cite a few epidemiological studies of occupational exposure to these metals and neurological outcomes (e.g., memory loss, slowed psychomotor functions), but no studies of neurodevelopmental outcomes in children. Toxicity of Cu, Mn, and Zn is not discussed in this article.	Reference does not support statement

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		Lucchini et al. (2017)	A book chapter on Mn (but not Cu or Zn) and developmental neurotoxicity. Several epidemiological studies are cited that show associations between Mn exposure and neurodevelopmental outcomes, although none measured Mn in meconium. Our systematic review of this topic (Leonhard et al. 2019) found that studies are mostly limited by their cross-sectional design and potential for confounding and selection bias, and that results are inconsistent and do not establish causal effects of environmental Mn exposure and neurodevelopmental toxicity.	Reference provides limited support regarding Mn (but not Cu or Zn), but does not capture state of science
The other metal that the EPA has episodically monitored is urinary As levels (The Butte-Silver Bow County Environmental Lead Study, Final Report, 1992), and in that case the Butte median was 23-fold higher, when compared to Columbia.	p. 3/5 to 4/1	The Butte-Silver Bow County Environmental Lead Study, Final Report, 1992	The Butte-Silver Bow County Environmental Lead Study showed no association of urinary arsenic with environmental exposure (i.e., arsenic in soil and dust). No data or reference are provided for Columbia for comparison. Urinary arsenic levels, even if speciated for inorganic arsenic and its metabolites can be greatly influenced by dietary arsenic forms.	Reference does not support statement
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper	p. 4/4	N/A	McDermott stated that her son, daughter-in-law, and granddaughter live in Butte, MT. Her son is Ted McDermott, a former reporter and editor at The Montana Standard. Though it would not be considered a conflict of interest, the Montana Standard also notes that McDermott and Hailer hope to use their findings on the 18 samples (of meconium) to apply for a large grant next year that would enable them to expand the research to a large sample size (https://mtstandard.com/news/local/brain-cancer-percent-higher-in-butte-and-anaconda-researcher-says/article_24782f34-9dd6-5baf-bc42-628a780a8ccc.html).	Declaration of Competing Interest is incomplete and potentially misleading

MIREC: Maternal-Infant Research on Environmental Chemicals

N/A: not applicable

Leonhard MJ, Chang ET, Loccisano AE, Garry MR. 2019. A systematic literature review of epidemiologic studies of developmental manganese exposure and neurodevelopmental outcomes. Toxicology. 2019; 420:46-65.